1: *Sarcoidosis Vasc Diffuse Lung Dis* 2000 Oct;17(3):271-6 Related Articles, Books

The value of interleukin-12 as an activity marker of pulmonary sarcoidosis.

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[Medline record in process]

BACKGROUND: Sarcoidosis is characterized by hyperactivity of T-helper lymphocytes and recent studies showed that they were mainly Th1 cells. IL-12 is a major cytokine inducing Th1 differentiation of naive T cells. This study was performed to test whether IL-12 can be a marker for disease activity and possibly a prognosis in sarcoidosis. METHODS: IL-12 levels of BALF (BALF-IL-12) and conditioned medium of alveolar macrophages (AM) were measured by ELISA in 36 patients with pulmonary sarcoidosis (14 males and 22 females, mean age: 39.6 +/- 11.0 years) and eleven normal controls. Clinically, 16 patients had active sarcoidosis and 20 had an inactive disease. RESULTS: BALF-IL-12 of sarcoidosis patients (41.3 +/- 43.9 pg/ml) was significantly higher than that of normal controls (2.5 +/- 0.4 pg/ml) ($p < 0.001$). The patients with active disease (71.3 +/- 54.3 pg/ml) had a higher BAL-IL-12 level than those with inactive disease (17.3 +/- 13.8 pg/ml) ($p = 0.0001$). It had a significant correlation with the number of T4 cells ($p = 0.0001$), total cell number, number and percentage of lymphocytes ($p = 0.0001$) and AM ($p = 0.001$) in BALF. It was also significantly correlated with soluble ICAM-1 levels in serum ($p = 0.0001$) and BALF ($p = 0.002$), and ICAM-1 expression of AM ($p = 0.001$). Furthermore the patients whose condition worsened without therapy had a significantly higher initial BALF-IL-12 level than the patients whose condition improved spontaneously. The AM of sarcoidosis secreted significantly more IL-12 (133 +/- 177 pg/ml) than AM of controls (68.3 +/- 43.7 pg/ml) ($p = 0.038$). CONCLUSION: Our data suggest that the BALF-IL-12 level can be used as a marker of the activity of pulmonary sarcoidosis and possibly prognosis.

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Antisense oligodeoxynucleotides to human inducible nitric oxide synthase selectively inhibit induced nitric oxide production by human vascular endothelial cells: an experimental study.

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[Medline record in process]

OBJECTIVE: To find out whether the antisense oligodeoxynucleotide designed against the complementary DNA to human inducible NO synthase (iNOS) would block the translation from iNOS mRNA to NO in human vascular endothelial cells. DESIGN: Prospective controlled study. SETTING: Research laboratory, Japan. MATERIAL: Cultured human vascular endothelial cells. INTERVENTIONS: Human vascular endothelial cells were cultured for 24 hours, and divided into two groups, one of which was exposed to antisense oligodeoxynucleotides and the other to sense oligodeoxynucleotides at 100, 200, 400 and 800 micromol/L, respectively, for 18 hours. They were then exposed to interferon-gamma (1000 units/ml) and recombinant human tumour necrosis factor alpha (500 units/ml) to stimulate NO production. Each experiment was repeated ten times. RESULTS: Clear bands expressing cDNA of iNOS mRNA were identified in agarose gels in all cultured cells in both groups. The mean nitrite concentration in the supernatants of cultured cells in the group with the addition of antisense oligodeoxynucleotides was significantly lower than that in the group with sense oligonucleotides added at 200, 400, and 800 micromol/L CONCLUSION: These findings indicate that the antisense oligodeoxynucleotides inhibited the NO production dependently, by preventing only their translation but not the processing, before their transcription from DNA into iNOS mRNA.

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1: *Anesthesiology* 2000 Jun;92(6):1702-12 Related Articles, Books, LinkOut

Sildenafil is a pulmonary vasodilator in awake lambs with acute pulmonary hypertension.

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BACKGROUND: Phosphodiesterase type 5 (PDE5) hydrolyzes cyclic guanosine monophosphate in the lung, thereby modulating nitric oxide (NO)/cyclic guanosine monophosphate-mediated pulmonary vasodilation. Inhibitors of PDE5 have been proposed for the treatment of pulmonary hypertension. In this study, we examined the pulmonary and systemic vasodilator properties of sildenafil, a novel selective PDE5 inhibitor, which has been approved for the treatment of erectile dysfunction. METHODS: In an awake lamb model of acute pulmonary hypertension induced by an intravenous infusion of the thromboxane analog U46619, we measured the effects of 12.5, 25, and 50 mg sildenafil administered via a nasogastric tube on pulmonary and systemic hemodynamics (n = 5). We also compared the effects of sildenafil (n = 7) and zaprinast (n = 5), a second PDE5 inhibitor, on the pulmonary vasodilator effects of 2.5, 10, and 40 parts per million inhaled NO. Finally, we examined the effect of infusing intravenous l-NAME (an inhibitor of endogenous NO production) on pulmonary vasodilation induced by 50 mg sildenafil (n = 6). RESULTS: Cumulative doses of sildenafil (12.5, 25, and 50 mg) decreased the pulmonary artery pressure 21%, 28%, and 42%, respectively, and the pulmonary vascular resistance 19%, 23%, and 45%, respectively. Systemic arterial pressure decreased 12% only after the maximum cumulative sildenafil dose. Neither sildenafil nor zaprinast augmented the ability of inhaled NO to dilate the pulmonary vasculature. Zaprinast, but not sildenafil, markedly prolonged the duration of pulmonary vasodilation after NO inhalation was discontinued. Infusion of l-NAME abolished sildenafil-induced pulmonary vasodilation. CONCLUSIONS: Sildenafil is a selective pulmonary vasodilator in an ovine model of acute pulmonary hypertension. Sildenafil induces pulmonary vasodilation via a NO-dependent mechanism. In contrast to zaprinast, sildenafil did not prolong the pulmonary vasodilator action of inhaled NO.